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A valuable heterocyclic ring transformation: from isoxazolin-5(2*H*)-ones to quinolines

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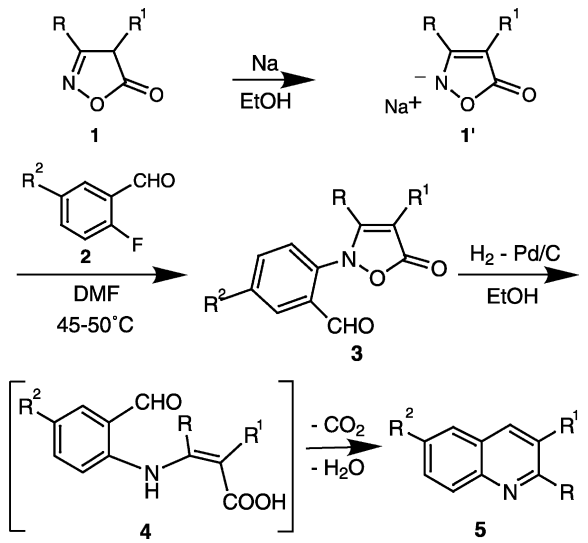
Abstract—A new synthesis of quinoline derivatives was achieved by catalytic hydrogenation of 3,4-disubstituted 2-(2-formylphenyl)-isoxazolin-5(2*H*)-ones. In the same way, 2,3-disubstituted [1,8]naphthyridine was obtained.

The development of new methods for the synthesis of nitrogen-containing heterocycles is of extreme importance in organic chemistry. We reported in the past years, the synthesis of pyrroles,[1] oxazinones,[2] imidazoles,[3] 2-pyrazinones,[4] isoxazoles[5] starting from isoxazolin-5-ones. As a part of our ongoing interest in the study of the reactivity of the isoxazolone nucleus as a synthon to obtain different heterocyclic systems, we describe now a new and easy approach to the quinoline nucleus starting from 2-aryl-3,4-disubstituted isoxazolin-5(2*H*)-ones. The presence of the quinoline scaffold in the framework of various pharmacologically active compounds with antiasthmatic,[6] antiinflammatory[7] and tyrosine kinase inhibiting properties[8] continues to spur synthetic efforts regarding their acquisition.[9]

The synthesis of quinolines has been a focus of organic chemistry for more than 100 years.[10] Most of the classical synthetic routes are limited to certain substitution patterns and suffer from harsh reaction conditions and poor yields. A precedent paper describing the synthesis of the 2,4-dichloroquinolines starting from 3-arylisoxazol-5(4*H*)-ones via Vilsmeier–Haack reaction is available.[11] The overall synthetic sequence to obtain quinolines consisted of three very simple steps: (a) isolation of the 3,4-disubstituted isoxazolin-5(2*H*)-one salt **1′a–g**; (b) nucleophilic substitution with the 2-fluorobenzaldehyde derivatives **2a** or **2b** to give the adducts **3**; (c) catalytic hydrogenation reaction to give directly the desired quinoline derivatives **5**.

Owing to the strong acidity of the isoxazolin-5(4*H*)-one nucleus, the reaction with a base (TEA or EtONa) gave the corresponding salt. On the basis of our research on the 5(2*H*)-isoxazolones as nucleophiles[12] we have considered the reaction of the isoxazolyl anion with a proper aryl halide in a nucleophilic aromatic substitution to give the 2-aryl derivatives **3** (Scheme 1 and Table 1). The nucleophilic substitution was possible only when the aryl halide was activated by an electron-withdrawing group in the *para* position to the halogen atom. The reaction was performed with 2-fluoro-5-nitrobenzaldehyde **2a** and with 2-fluoro-5-trifluoromethylbenzaldehyde **2b**. Better yields were obtained with **2a** in comparison to **2b**.

It is known that catalytic hydrogenation of the isoxazolin-5-ones favours the N–O bond cleavage.[13] Consequently, the ring opening gave the enamine intermediate **4** susceptible to



Scheme 1.

Keywords: quinolines; isoxazolones; catalytic hydrogenation; naphthyridine.
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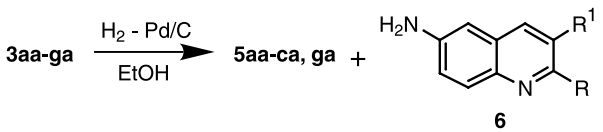
Table 1. Data for Scheme 1

Substrate	R	R^1	Substrate	R^2	Product	Yield (%)
1a	CH_3	CH_2Ph	**2a**	NO_2	**3aa**	99
1b	CH_3	Ph	**2a**	NO_2	**3ba**	78
1c	$CH_2CH_2CH_3$	CH_2Ph	**2a**	NO_2	**3ca**	70
1d	Ph	CH_3	**2a**	NO_2	**3da**	95
1e	Ph	CH_2CH_3	**2a**	NO_2	**3ea**	83
1f	$-(CH_2)_4-$		**2a**	NO_2	**3fa**	99
1g	$-CH_2CH_2SCH_2-$		**2a**	NO_2	**3ga**	87
1a	CH_3	CH_2Ph	**2b**	CF_3	**3ab**	70
1b	CH_3	Ph	**2b**	CF_3	**3bb**	75
1c	$CH_2CH_2CH_3$	CH_2Ph	**2b**	CF_3	**3cb**	68
1d	Ph	CH_3	**2b**	CF_3	**3db**	62
1e	Ph	CH_2CH_3	**2b**	CF_3	**3eb**	68
1f	$-(CH_2)_4-$		**2b**	CF_3	**3fb**	67
1g	$-CH_2CH_2SCH_2-$		**2b**	CF_3	**3gb**	68

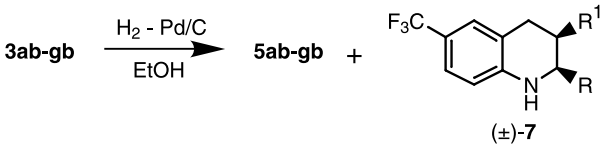
decarboxylation and subsequent intramolecular cyclocondensation on the formyl group. The hydrogenation reaction was performed with different catalysts and solvents. Better yields were obtained with palladium on charcoal in ethanol as a solvent. In the case of the substrates **3aa**–**ga** containing the nitro group, in all conditions, the 6-aminoquinoline derivatives **6** were obtained as major product, accompanied by a minor amount of the quinolines **5**. In the case of substrates **3da**, **3ea**, **3ga** only the corresponding aminoquinolines **6da**, **6ea** and **6ga** were isolated (Scheme 2 and Table 2).



Scheme 2.

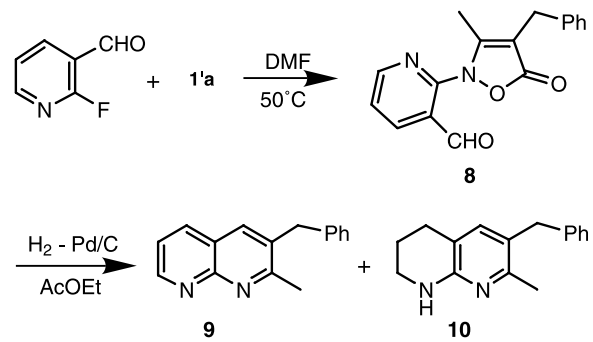
Only in the case of compound **3ga** containing a sulfur atom, the quinoline **5ga** was the only product. With the substrates **3ab**-**gb** including the trifluoromethyl group on the aromatic ring, besides the desired quinolines **5** tetrahydroquinolines **7** were also isolated, with the exception of **5gb** (Scheme 3 and Table 2). The relative configuration of the two stereocentres was assumed to be *cis* on the basis of the vicinal coupling constants, whenever detectable.[14]

With the aim to extend the synthetic procedure for the preparation of different heterocyclic systems, the reaction



Scheme 3.

was tested with the isoxazolone salt **1′a** and 2-fluoro-3-formylpyridine. The adduct **8** was submitted to the hydrogenation process and the reaction gave the [1,8]naphthyridine **9** in good yield. Besides the fully aromatic product, the reductive process gave also the [1,8]tetrahydronaphthyridine **10** arising from the partial hydrogenation of the pyridine ring (Scheme 4). The ratio between the two products depends on the reaction conditions. Performing the hydrogenation with Pd/C in ethyl acetate the ratio was 6:1 in favour of the naphthyridine **9**, with Pd/C in ethanol the result was opposite with a ratio 1:3 in favour of the tetrahydronaphthyridine **10**.



Scheme 4.

In conclusion, this paper shows a new and easy synthetic pathway to the quinoline system allowing a very large substitution patterns. Furthermore, starting from suitable substrate, the synthesis of other heterocyclic systems is possible.

1. Experimental

1.1. General

Melting points were determined on a Buchi 510 or an

Table 2. Data for Schemes 2 and 3

Substrate	R	R^1	Product **5**	Yield (%)	Product **6**	Yield (%)	Product **7**	Yield (%)
3aa	CH_3	CH_2Ph	**5aa**	8	**6aa**	84		
3ba	CH_3	Ph	**5ba**	6	**6ba**	66		
3ca	$CH_2CH_2CH_3$	CH_2Ph	**5ca**	10	**6ca**	64		
3da	Ph	CH_3	**5da**	–	**6da**	97		
3ea	Ph	CH_2CH_3	**5ea**	–	**6ea**	98		
3fa	$-(CH_2)_4-$		**5fa**	–	**6fa**	55		
3ga	$-CH_2CH_2SCH_2-$		**5ga**	84	**6ga**	–		
3ab	CH_3	CH_2Ph	**5ab**	45			**7ab**	14
3bb	CH_3	Ph	**5bb**	41			**7bb**	41
3cb	$CH_2CH_2CH_3$	CH_2Ph	**5cb**	58			**7cb**	23
3db	Ph	CH_3	**5db**	38			**7db**	48
3eb	Ph	CH_2CH_3	**5eb**	61			**7eb**	28
3fb	$-(CH_2)_4-$		**5fb**	32			**7fb**	40
3gb	$-CH_2CH_2SCH_2-$		**5gb**	77			**7gb**	–

Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Jasco IR Report 100 spectrophotometer, in nujol mull for solids and as a liquid film for oils. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200, Bruker AC 200 and Bruker Avance 300 spectrometer in $CDCl_3$ solution unless otherwise stated. Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator.

Compounds **1a**,[15] **1b**,[16] **1c**,[17] **1d**,[18] **1e**,[19] **1f**,[20] were prepared according to the literature procedures.

1.1.1. Synthesis of 1,4,6,7-tetrahydrothiopyrano[4,3-*c*]isoxazol-3-one 1g. To a solution of 4-oxo-tetrahydro-thiopyran-3-ethylcarboxylate[21] (5.6 g, 30 mmol) in EtOH (80 ml) a mixture of hydroxylamine hydrochloride (3.12 g, 45 mmol) and AcONa (3.69 g, 45 mmol) in water (20 ml) was added. After heating to reflux for 2 h, the solvent was evaporated, water was added (60 ml) and the mixture extracted with CH_2Cl_2 (2×40 ml). The organic layer was dried, filtered and evaporated and the residue purified by silica gel column chromatography, eluent CH_2Cl_2 to give **1g**, 90% yield, mp 107–108°C (white crystals from CH_2Cl_2–hexane); IR 1720, 1692 cm^{-1}; ^{1}H NMR (CD_3COCD_3): 2.78 (t, 2H, *J*=5.5 Hz), 2.96 (t, 2H, *J*=5.5 Hz), 3.29 (s, 2H), 10.30 (br s, 1H, D_2O); ^{13}C NMR (CD_3COCD_3): 19.7, 23.8, 23.9 (CH_2), 96.6, 164.7 (C), 170.4 (CO). Anal. calcd for $C_6H_7NO_2S$: C, 45.86; H, 4.46; N, 8.92. Found: C, 45.69; H, 4.52; N, 8.80.

1.1.2. Sodium salts 1′ of 3,4-disubstituted 5(2*H*)-isoxazolones 1: general procedure. A methanolic solution of NaOMe, prepared from MeOH (5 ml) and Na (92 mg, 4 mmol) was added to a solution of the isoxazolin-5-one **1** (4 mmol) in MeOH (10 ml). After evaporation of the solvent, the residue was dried for 1 h at 60°C/5 mbar.

1.1.3. Synthesis of 2-aryl-3,4-disubstituted isoxazolin-5(2*H*)-ones 3: general procedure. To a solution of isoxazolin-5(2*H*)-ones sodium salt **1′** (2 mmol) in DMF (3 ml), the 5-substituted-2-fluorobenzaldehyde **2a** or **2b** (3 mmol) was added. The mixture was heated to 45–50°C under stirring for the reported time (see below) and diluted with brine: (i) for the compounds **3aa**–**ga**, the solid formed was filtered and purified by crystallization, (ii) for the compounds **3ab**–**gb**, the mixture was extracted with Et_2O (2×20 ml), the organic layer dried (Na_2SO_4), filtered, evaporated and the residue purified by crystallization or by silica gel column chromatography (eluent see below).

From **1a** and **2a**, heated for 0.5 h, **3aa**, mp 46–47°C (yellow crystals from hexane); IR: 1748, 1698, 1610, 1490 cm^{-1}; ^{1}H NMR: 3.72 (s, 3H), 5.32 (s, 2H), 7.33 (m, 5H), 7.46 (d, 1H, *J*=8.8 Hz), 8.52 (dd, 1H, *J*=2.5, 8.8 Hz), 8.86 (d, 1H, *J*=2.5 Hz), 10.45 (s, 1H); ^{13}C NMR: 16.8 (CH_3), 29.2 (CH_2), 116.8, 122.6, 125.5, 127.2 (CHAr), 128.4 (2×CHAr), 129.2 (2×CHAr), 127.3, 130.2, 137.7, 143.6, 154.2, 158.2 (C), 168.5 (CO), 186.2 (CHO). Anal. calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.79; H, 4.33; N, 8.23.

From **1b** and **2a**, heated for 2 h, **3ba**, mp 154–156°C (orange crystals from Et_2O); IR: 1720, 1686, 1613, 1530, 1377 cm^{-1}; ^{1}H NMR: 2.31 (s, 3H), 7.41–7.65 (m, 6H), 8.58 (dd, 1H, *J*=2.5, 8.8 Hz), 8.91 (d, 1H, *J*=2.5 Hz), 10.51 (s, 1H); ^{13}C NMR: 13.5 (CH_3), 124.9, 129.5 (CHAr), 127.4 (2×CHAr), 128.6 (2×CHAr), 129.1 (2×CHAr), 107.5, 128.3, 133.2, 144.1, 148.3, 158.8 (C), 168.7 (CO), 186.7 (CHO). Anal. calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 63.03; H, 3.80; N, 8.52.

From **1c** and **2a**, heated for 2 h, **3ca**, mp 85–87°C (yellow crystals from Et_2O–hexane); IR: 1722, 1613, 1528 cm^{-1}; ^{1}H NMR: 0.82 (t, 3H, *J*=7.3 Hz), 1.20–1.40 (m, 2H), 2.36 (t, 2H, *J*=7.3 Hz), 3.75 (s, 2H), 7.33 (m, 5H), 7.40 (d, 1H, *J*=8.8 Hz), 8.52 (dd, 1H, *J*=2.5, 8.8 Hz); 8.87 (d, 1H, *J*=2.5 Hz), 10.51 (s, 1H); ^{13}C NMR 14.1 (CH_3), 21.6, 28.5, 28.8 (CH_2), 124.6, 127.3, 127.8, 129.2, 129.3, 129.6 (CHAr), 128.6 (2×CHAr), 107.7, 134.2, 138.3, 145.6, 148.8, 154.8 (C), 164.8 (CO), 186.9 (CHO). Anal. calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.42; H, 5.03; N, 7.60.

From **1d** and **2a**, heated for 2 h, **3da**, mp 153–155°C dec. (light yellow crystals from Et_2O); IR: 1724, 1681, 1622, 1519, 1380 cm^{-1}; ^{1}H NMR: 2.14 (s, 3H), 7.06 (d, 1H, *J*=8.8 Hz), 7.42 (m, 2H), 7.50 (m, 3H), 8.26 (dd, 1H, *J*=2.5, 8.8 Hz), 8.80 (d, 1H, *J*=2.5 Hz), 10.68 (s, 1H); ^{13}C NMR: 11.2 (CH_3), 105.3, 124.5, 134.9, 145.2, 146.9, 157.3 (C), 116.8, 122.6, 127.2, 127.7 (CHAr), 126.2 (2×CHAr), 128.4 (2×CHAr), 170.3 (CO), 186.4 (CHO). Anal. calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 62.80; H, 3.89; N, 8.48.

From **1e** and **2a**, heated for 24 h, **3ea**, mp 143–145°C (light yellow crystals from Et_2O–hexane); IR: 1740, 1682, 1530, 1377 cm^{-1}; ^{1}H NMR: 1.28 (t, 3H, *J*=7.3 Hz), 2.54 (q, 2H, *J*=7.3 Hz), 7.09 (d, 1H, *J*=8.4 Hz), 7.38 (m, 2H), 7.50 (m, 3H), 8.24 (dd, 1H, *J*=2.5, 8.4 Hz), 8.78 (d, 1H, *J*=2.5 Hz), 10.64 (s, 1H); ^{13}C NMR: 13.3 (CH_3), 16.4 (CH_2), 111.2, 127.2, 133.0, 146.0, 147.4, 160.3 (C), 124.1, 126.5, 126.9, 128.3, 129.8, 131.6 (CHAr), 128.8 (2×CHAr), 170.1 (CO), 186.6 (CHO). Anal. calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 64.08; H, 4.31; N, 8.15.

From **1f** and **2a**, heated for 5 h, **3fa**, mp 156°C dec. (cream crystals from acetone); IR: 1749, 1688, 1377 cm^{-1}; ^{1}H NMR (CD_3OD): 1.83 (m, 4H), 2.86 (m, 4H), 7.51 (d, 1H, *J*=8.8 Hz), 8.33 (dd, 1H, *J*=2.6, 8.8 Hz), 8.64 (d, 1H, *J*=2.6 Hz), 10.56 (s, 1H); ^{13}C NMR: 18.3, 21.3, 21.7, 22.7 (CH_2), 92.8, 122.7, 124.4 (CHAr), 101.8, 140.8, 141.8, 148.8, 165.5 (C), 171.3 (CO), 186.9 (CHO). Anal. calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72: Found: C, 58.20; H, 4.29; N, 9.73.

From **1g** and **2a**, heated for 5 h, **3ga**, mp 125–127°C (ochre crystals from AcOEt–hexane); IR:1722, 1672, 1590, 1380 cm^{-1}; ^{1}H NMR: 2.59 (t, 2H, *J*=5.9 Hz), 2.90 (t, 2H, *J*=5.9 Hz), 3.52 (s, 2H), 7.56 (d, 1H, *J*=8.8 Hz), 8.56 (dd, 1H, *J*=2.5, 8.8 Hz), 8.87 (d, 1H, *J*=2.5 Hz), 10.44 (s, 1H); ^{13}C NMR: 19.9, 23.9, 25.3 (CH_2), 101.7, 133.0, 144.5, 148.3, 163.4 (C), 124.1, 127.5, 129.1 (CHAr), 168.1 (CO), 187.7 (CHO). Anal. calcd for $C_{13}H_{10}N_2O_5S$: C, 50.98; H, 3.29; N, 9.15. Found: C, 50.91; H, 3.41; N, 9.08.

From **1a** and **2b**, heated for 24 h, SiO_2 eluent: hexane–Et_2O

2:1, **3ab**, mp 154–156°C (cream crystals from AcOEt); IR: 1730, 1612, 1463, 1374 cm^{-1}; ^1H NMR: 2.04 (s, 3H), 3.72 (s, 2H), 7.27–7.34 (m, 5H), 7.39 (d, 1H, *J*=8.4 Hz), 7.95 (dd, 1H, *J*=2.2, 8.4 Hz), 8.31 (d, 1H, *J*=2.2 Hz), 10.47 (s, 1H). ^{13}C NMR: 13.5 (CH_3), 28.4 (CH_2), 106.5, 133.1, 127.8, 144.2, 160.3 (C), 123.1 (CF_3), 132.4 (C–CF_3), 126.7, 127.1, 128.5, 131.8 (CHAr), 128.3 (2×CHAr), 129.6 (2×CHAr), 169.3 (C═O), 187.6 (CHO). Anal. calcd for $C_{19}H_{14}F_3NO_3$: C, 63.16; H, 3.91; N, 3.88. Found: C, 63.17; H, 3.77; N, 4.03.

From **1b** and **2b**, heated for 24 h, SiO_2 eluent: hexane–Et_2O 3:1, **3bb**, mp 99°C (orange crystals from Et_2O); IR: 1732, 1698, 1613 cm^{-1}; ^1H NMR: 2.28 (s, 3H), 7.38–7.59 (m, 6H), 8.01 (d, 1H, *J*=8.2 Hz), 8.33 (s, 1H), 10.47 (s, 1H); ^{13}C NMR: 13.4 (CH_3), 122.9 (CF_3), 126.6, 127.1, 128.4, 131.8 (CHAr), 128.3 (2×CHAr), 128.9 (2×CHAr), 106.7, 133.3, 126.9, 142.4, 159.1 (C), 132.7 (C–CF_3), 168.9 (C═O), 187.4 (CHO). Anal. calcd for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03; Found: C, 62.31; H, 3.51; N, 4.08.

From **1c** and **2b**, heated for 5 h, SiO_2 eluent: hexane–CH_2Cl_2 10:1 to CH_2Cl_2, **3cb**, mp 91–93°C (white crystals from hexane–Et_2O); IR: 1746, 1698, 1613 cm^{-1}; ^1H NMR: 0.89 (t, 3H, *J*=7.3 Hz), 1.35 (tq, 2H, *J*=7.3, 7.3 Hz), 2.34 (t, 2H, *J*=7.3 Hz), 3.74 (s, 2H), 7.26–7.40 (m, 6H), 7.95 (dd, 1H, *J*=1.8, 8.4 Hz), 8.32 (d, 1H, *J*=1.8 Hz), 10.51 (s, 1H); ^{13}C NMR: 13.9 (CH_3), 21.5, 28.3, 28.6 (CH_2), 107.0, 133.8, 138.4, 143.7, 165.1 (C), 123.0 (CF_3), 126.4, 127.1, 127.4, 131.9 (CHAr), 128.5 (2×CHAr), 129.1 (2×CHAr), 131.1 (C–CF_3), 171.2 (C═O), 187.7 (CHO). Anal. calcd for $C_{21}H_{18}F_3NO_3$: C, 64.78; H, 4.66; N, 3.60. Found: C, 64.86; H, 4.81; N, 3.46.

From **1d** and **2b**, heated for 1 h, SiO_2 eluent: hexane–Et_2O 3:1, **3db**, mp 98–100°C (white crystals from hexane); IR: 1722, 1690, 1608 cm^{-1}; ^1H NMR: 2.13 (s, 3H), 7.02 (d, 1H, *J*=8.4 Hz), 7.37–7.49 (m, 5H), 7.68 (dd, 1H, *J*=2.2, 8.4 Hz), 8.25 (d, 1H, *J*=2.2 Hz), 10.73 (s, 1H); ^{13}C NMR: 8.3 (CH_3), 105.8, 133.2, 127.8, 144.9, 161.1 (C), 123.1 (CF_3), 132.0 (C–CF_3), 126.2, 126.7, 131.4, 131.6 (CHAr), 128.5 (2×CHAr), 129.8 (2×CHAr), 171.1 (C═O), 187.8 (CHO). Anal. calcd for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03; Found: C, 62.37; H, 3.53; N, 3.84.

From **1e** and **2b**, heated for 2 h, SiO_2 eluent: hexane–CH_2Cl_2 1:1, **3eb**, mp 114–116°C (white crystals from Et_2O–hexane); IR: 1737, 1698, 1607 cm^{-1}; ^1H NMR: 1.28 (t, 3H, *J*=7.3 Hz), 2.54 (q, 2H, *J*=7.3 Hz), 7.05 (d, 1H, *J*=8.4 Hz), 7.38–7.49 (m, 5H), 7.70 (dd, 1H, *J*=1.8, 8.4 Hz), 8.23 (d, 1H, *J*=1.8 Hz), 10.69 (s, 1H); ^{13}C NMR: 13.4 (CH_3), 16.4 (CH_2), 110.8, 129.1, 128.9, 144.6, 160.9 (C), 126.0, 126.4, 131.2, 131.4 (CHAr), 128.3 (2×CHAr), 129.7 (2×CHAr), 123.1 (CF_3), 132.9 (C–CF_3), 170.6 (C═O), 187.6 (CHO). Anal. calcd for $C_{19}H_{14}F_3NO_3$: C, 63.16; H, 3.91; N, 3.88. Found: C, 63.25; H, 3.99; N, 3.90.

From **1f** and **2b**, heated for 2 h, SiO_2 eluent: hexane–CH_2Cl_2 1:1, **3fb**, mp 117–119°C (cream crystals from Et_2O); IR: 1754, 1613 cm^{-1}; ^1H NMR: 1.82 (m, 4H), 2.27 (m, 2H), 2.42 (m, 2H), 7.48 (d, 1H, *J*=8.4 Hz), 7.95 (dd, 1H, *J*=1.8, 8.4 Hz), 8.31 (d, 1H, *J*=1.8 Hz), 10.40 (s, 1H); ^{13}C NMR: 18.8, 21.5, 21.6, 23.3 (CH_2), 105.3, 131.4, 143.9, 164.2 (C), 123.2 (CF_3), 131.8 (C–CF_3), 125.4, 126.3, 131.9 (CHAr), 170.2 (C═O), 187.7 (CHO). Anal. calcd for $C_{15}H_{12}F_3NO_3$: C, 57.88; H, 3.89; N, 4.50. Found: C, 57.98; H, 3.94; N, 4.36.

From **1g** and **2b**, heated for 5 h, SiO_2 eluent: hexane–Et_2O 1:1, **3gb**, mp 95–98°C (ochre crystals from Et_2O–hexane); IR: 1730, 1679, 1630, 1597 cm^{-1}; ^1H NMR: 2.56 (t, 2H, *J*=5.8 Hz), 2.93 (t, 2H, *J*=5.8 Hz), 3.58 (s, 2H), 7.54 (d, 1H, *J*=8.4 Hz), 8.02 (dd, 1H, *J*=2.2, 8.4 Hz), 8.37 (d, 1H, *J*=2.2 Hz), 10.41 (s, 1H); ^{13}C NMR: 20.6, 24.5, 25.5 (CH_2), 103.3, 132.7, 133.0, 143.1, 163.3 (C), 123.2 (CF_3), 126.5, 126.8, 132.2 (C–CF_3), 168.9 (C═O), 187.6 (CHO). Anal. calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.06; H, 3.06; N, 4.25. Found: C, 51.14; H, 3.21; N, 4.30.

1.1.4. Synthesis of quinolines 5, 6 and tetrahydroquinolines 7: general procedure. The compound **3** (1 mmol) was dissolved in EtOH (15 ml), 10% Pd/C (40 mg) was added and the mixture hydrogenated under atmospheric pressure at rt. After 5 h the catalyst was filtered off, the solvent evaporated and the crude material was crystallized or chromatographed (see below).

From **3aa**, reaction time 6 h, SiO_2 eluent: CH_2Cl_2–Et_2O 1:1, afforded compounds **5aa**, mp 190°C (beige crystals from Et_2O–hexane); IR: 1442, 1360 cm^{-1}; ^1H NMR: 2.77 (s, 3H), 4.21 (s, 2H), 7.20 (m, 2H), 7.36 (m, 3H), 7.92 (s, 1H), 8.17 (d, 1H, *J*=9.1 Hz), 8.44 (dd, 1H, *J*=2.5, 9.1 Hz), 8.70 (d, 1H, *J*=2.5 Hz); ^{13}C NMR: 24.4 (CH_3), 39.4 (CH_2), 122.7, 124.4, 127.3, 130.4, 137.3 (CHAr), 129.3 (2×CHAr), 128.5 (2×CHAr), 126.4, 135.7, 138.2, 145.5, 149.1, 163.6 (C). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.45; H, 5.17; N, 9.98; and **6aa**, mp 195–196°C (ochre crystals from Et_2O–hexane). IR: 3230, 3140, 1620, 1597, 1440 cm^{-1}; ^1H NMR: 2.62 (s, 3H), 3.90 (br s, 2H, D_2O), 4.11 (s, 2H), 6.84 (d, 1H, *J*=2.5 Hz), 7.20 (m, 3H), 7.30 (m, 3H), 7.58 (s, 1H), 7.90 (d, 1H, *J*=8.8 Hz); ^{13}C NMR: 24.9 (CH_3), 39.2 (CH_2), 107.2, 120.8, 125.5, 127.9, 125.5, 127.9, 128.4, 129.2, 134.5 (CHAr), 128.5, 135.1, 137.4, 141.9, 144.7, 155.9 (C). Anal. calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.09; H, 6.42; N, 11.15.

From **3ba**, reaction time 2 h, SiO_2 eluent: from hexane to Et_2O, afforded compounds **5ba**, mp 190°C (yellow crystals from Et_2O–hexane); IR: 1601, 1521, 1376 cm^{-1}; ^1H NMR: 2.74 (s, 3H), 7.40–7.55 (m, 5H), 8.14 (s, 1H), 8.18 (d, 1H, *J*=9.1 Hz), 8.48 (dd, 1H, *J*=2.5, 9.1 Hz), 8.79 (d, 1H, *J*=2.5 Hz); ^{13}C NMR: 25.4 (CH_3), 123.2, 124.7, 129.4, 130.6, 137.7 (CHAr), 128.7 (2×CHAr), 129.1, (2×CHAr), 126.1, 138.2, 139.0, 145.6, 149.4, 162.4 (C). Anal. calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.81; H, 4.73; N, 10.31; and **6ba** mp 122–124°C (cream crystals from Et_2O–hexane); IR: 3318, 3191, 1628, 1462, 1377 cm^{-1}; ^1H NMR: 2.64 (s, 3H), 3.90 (br s, 2H, D_2O), 6.91 (d, 1H, *J*=2.5 Hz), 7.18 (dd, 1H, *J*=2.5, 9.1 Hz), 7.40–7.75 (m, 5H), 7.77 (s, 1H), 7.94 (d, 1H, 9.1 Hz); ^{13}C NMR: 24.3 (CH_3), 107.8, 121.9, 128.4, 128.7, 134.8 (CHAr), 127.0 (2×CHAr), 129.1 (2×CHAr), 129.2, 136.4, 140.6, 142.3, 144.7, 153.7 (C). Anal. calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.16; H, 6.11; N, 11.81.

From **3ca**, reaction time 4 h, SiO_2 eluent: hexane–Et_2O 1:1,

afforded compounds **5ca**, mp 135–138°C (yellow crystals from Et_2O–hexane); IR: 1599, 1380 cm^{-1};^1H NMR: 1.05 (t, 3H, *J*=7.3 Hz), 1.83 (tq, 2H, *J*=7.3, 7.3 Hz), 3.00 (t, 2H, *J*=7.3 Hz), 4.24 (s, 2H), 7.20 (m, 2H), 7.38 (m, 3H), 7.90 (s, 1H), 8.17 (d, 1H, *J*=9.1 Hz), 8.42 (dd, 1H, *J*=2.5, 9.1 Hz), 8.67 (d, 1H, *J*=2.5 Hz); ^{13}C NMR: 14.6 (CH_3), 22.5, 38.6, 38.9 (CH_2), 122.6, 124.4, 127.3, 129.3, 129.4, 130.6, 137.8 (CHAr), 129.2 (2×CHAr), 126.2, 135.4, 18.7, 145.4, 149.2, 166.8 (C). Anal. calcd for $C_{19}H_{18}N_2O_2$: C, 74.49, H, 5.92; N, 9.14. Found: C, 74.60; H, 5.99; N, 9.05; and **6ca**, mp 163–165°C (beige from Et_2O–hexane); IR: 3405, 3250, 1610, 1580, 1440 cm^{-1}; ^1H NMR: 1.02 (t, 3H, *J*=7.3 Hz), 1.74 (tq, 2H, *J*=7.3, 7.3 Hz), 2.91 (t, 2H, *J*=7.3 Hz), 3.93 (br s, 2H, D_2O), 4.15 (s, 2H), 6.82 (d, 1H, *J*=2.2 Hz), 7.15 (m, 3H), 7.30 (m, 3H), 7.59 (s, 1H), 7.96 (d, 1H, *J*=9.1 Hz); ^{13}C NMR: 14.7 (CH_3), 23.2, 38.2, 39.1 (CH_2), 107.6, 121.2, 126.7, 128.8, 128.9, 129.2, 129.3, 129.9, 134.9 (CHAr), 129.1, 133.0, 140.1, 142.0, 144.4, 158.8 (C). Anal. calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.66; H, 7.38; N, 10.02.

From **3da**, reaction time 6 h, SiO_2 eluent: CH_2Cl_2–Et_2O 1:1, afforded compound **6da**, mp 150–152°C (ochre crystals from Et_2O–hexane); IR: 3410, 3240, 1640, 1557 cm^{-1}; ^1H NMR: 2.42 (s, 3H), 3.90 (br s, 2H, D_2O), 6.88 (d, 1H, *J*=2.5 Hz), 7.14 (dd, 1H, *J*=2.5, 9.1 Hz), 7.48 (m, 3H), 7.60 (m, 2H), 7.83 (s, 1H), 8.04 (dd, 1H, *J*=2.5, 9.1 Hz); ^{13}C NMR: 21.0 (CH_3), 107.0, 121.3, 129.3, 130.8, 135.0 (CHAr), 128.6 (2×CHAr), 128.2 (2×CHAr), 129.8, 129.5, 141.5, 142.2, 145.0, 157.3 (C). Anal. calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.11; H, 6.09; N, 11.82.

From **3ea**, reaction time 3 h, SiO_2 eluent: CH_2Cl_2–Et_2O 1:1, afforded compound **6ea**, mp 160–162°C (beige crystals from Et_2O–hexane); IR: 3328, 3212, 1620, 1454 cm^{-1}; ^1H NMR: 1.19 (t, 3H, *J*=7.3 Hz), 2.77 (q, 2H, *J*=7.3 Hz), 2.98 (br s, 2H, D_2O), 6.93 (d, 1H, *J*=2.2 Hz), 7.16 (dd, 1H, *J*=2.2, 9.1 Hz), 7.50 (m, 5H), 7.87 (s, 1H), 8.07 (d, 1H, *J*=9.1 Hz) manca 1H; ^{13}C NMR: 16.5 (CH_3), 22.6 (CH_2), 107.2, 121.5, 127.2, 128.5, 135.3 (CHAr), 127.1 (2×CHAr), 129.0 (2×CHAr), 129.9, 141.5, 142.5, 144.7, 157.6 (C). Anal. calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.30; H, 6.58; N, 11.08.

From **3fa**, reaction time 5 h, SiO_2 eluent: from CH_2Cl_2–AcOEt 3:1 to AcOEt, afforded compound **6fa**,[22] mp 111–112°C (beige crystals from *i*-Pr_2O); IR: 3329, 3198, 1634, 1457 cm^{-1}; ^1H NMR: 1.93 (m, 4H), 2.94 (t, 2H, *J*=6.6 Hz), 3.08 (t, 2H, *J*=6.6 Hz), 3.80 (br s, 2H, D_2O), 6.83 (d, 1H, *J*=2.6 Hz), 7.08 (dd, 1H, *J*=2.6, 8.8 Hz), 7.59 (s, 1H), 7.81 (d, 1H, *J*=8.8 Hz); ^{13}C NMR: 23.4, 23.7, 29.7, 33.5 (CH_2), 107.3, 121.3, 129.6, 133.4 (CHAr), 128.9, 131.6, 142.1, 144.2, 155.8 (C). Anal. calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.83; H, 7.19; N, 14.04.

From **3ga**, reaction time 6 h, afforded compound **5ga**, mp 168–170°C (ochre crystals from CH_2Cl_2–pentane); IR: 1580, 1530 cm^{-1}; ^1H NMR: 3.16 (t, 2H, *J*=6.3 Hz), 3.48 (t, 2H, *J*=6.3 Hz), 4.00 (s, 2H), 8.06 (s, 1H), 8.14 (d, 1H, *J*=9.3 Hz), 8.45 (dd, 1H, *J*=2.4, 9.3 Hz), 8.76 (d, 1H, *J*=2.4 Hz); ^{13}C NMR: 26.0, 26.4, 34.8 (CH_2), 122.5, 124.7, 130.6, 135.2 (CHAr), 126.5, 132.4, 146.2, 149.3, 163.0 (C). Anal. calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.66; H, 4.17; N, 11.30.

From **3ab**, reaction time 4 h, SiO_2 eluent: from CH_2Cl_2–hexane 1:1 to CH_2Cl_2–Et_2O, afforded compounds **5ab**, mp 84–86°C (cream crystals from hexane); IR: 1452 cm^{-1}; ^1H NMR: 2.72 (s, 3H), 4.19 (s, 2H), 7.20 (m, 2H), 7.38 (m, 3H), 7.82 (m, 2H), 8.04 (s, 1H), 8.13 (d, 1H, *J*=8.8 Hz); ^{13}C NMR: 24.0 (CH_3), 39.3 (CH_2), 124.4 (CF_3), 124.8, 125.4, 127.0, 129.7, 136.5 (CHAr), 129.1 (2×CHAr), 129.2 (2×CHAr), 127.9 (C–CF_3), 126.3, 134.7, 138.4, 147.8, 161.7 (C). Anal. calcd for $C_{18}H_{14}F_3N$: C, 71.75; H, 4.68, N, 4.65. Found: C, 71.86; H, 4.77; N, 4.63; and **7ab**, oil; IR: 3413, 1619, 1519 cm^{-1}; ^1H NMR: 1.26 (d, 3H, *J*=6.6 Hz), 2.20–2.80 (m, 5H), 3.60 (m, 1H), 4.16 (br s, 1H, D_2O), 6.49 (d, 1H, *J*=8.4 Hz), 7.15–7.37 (m, 7H); ^{13}C NMR: 22.2 (CH_3), 31.0, 34.7 (CH_2), 38.9, 54.7 (CH), 112.9, 124.2, 126.9, 127.2 (CHAr), 128.5 (2×CHAr), 128.7 (2×CHAr), 118.8 (CF_3), 121.9 (C–CF_3), 123.8, 140.9, 146.6 (C). Anal. calcd for $C_{18}H_{18}F_3N$: C, 70.81; H, 5.94; N, 4.59. Found: C, 70.92; H, 5.99; N, 4.52.

From **3bb**, reaction time 12 h, SiO_2 eluent: from CH_2Cl_2–hexane 1:10 to CH_2Cl_2, afforded compounds **5bb**, mp 156–158°C (yellow crystals from Et_2O–hexane); IR: 1450 cm^{-1}; ^1H NMR: 2.72 (s, 3H), 7.40–7.53 (m, 5H), 7.91 (dd, 1H, *J*=1.9, 8.8 Hz), 8.06 (s, 1H), 8.13 (d, 1H, *J*=1.9 Hz), 8.18 (d, 1H, *J*=8.8 Hz); ^{13}C NMR: 24.9 (CH_3), 122.9 (CF_3), 125.1, 125.3, 128.3, 129.7, 137.0 (CHAr), 128.8 (2×CHAr), 129.3 (2×CHAr), 126.1 (C–CF_3), 127.9, 137.4, 139.3, 148.1, 160.4 (C). Anal. calcd for $C_{17}H_{12}F_3N$: C, 71.08; H, 4.21; N, 4.88. Found: C, 71.19; H, 4.29; N, 4.99; and **7bb**, oil; IR: 3411, 1620, 1521 cm^{-1}; ^1H NMR: 0.99 (d, 3H, *J*=6.6 Hz), 3.14 (m, 2H), 3.25 (m, 1H), 3.78 (m, 1H), 4.25 (br s, 1H, D_2O), 6.56 (d, 1H, *J*=8.8 Hz), 7.17–7.35 (m, 7H); ^{13}C NMR: 19.9 (CH_3), 33.1 (CH_2), 46.3, 59.2 (CH), 113.0, 124.2, 126.3, 127.3 (CHAr), 128.5 (2×CHAr), 128.9 (2×CHAr), 119.2 (CF_3), 120.6 (C–CF_3), 123.5, 141.2, 146.2 (C). Anal. calcd for $C_{17}H_{16}F_3N$: C, 70.09; H, 5.54; N, 4.81. Found: C, 69.93; H, 5.73; N, 4.70.

From **3cb**, reaction time 6 h, SiO_2 eluent: CH_2Cl_2–hexane 1:2, afforded compounds **5cb**, mp 68–69°C (beige crystals from hexane); IR: 1449 cm^{-1}; ^1H NMR: 1.04 (t, 3H, *J*=7.3 Hz), 1.81 (tq, 2H, *J*=7.3, 7.3 Hz), 2.99 (t, 2H, *J*=7.3 Hz), 4.23 (s, 2H), 7.20 (m, 2H), 7.34 (m, 3H), 7.82 (m, 2H), 8.03 (s, 1H), 8.18 (d, 1H, *J*=9.1 Hz); ^{13}C NMR: 14.2 (CH_3), 23.2, 38.2, 39.2 (CH_2), 124.2, 125.2, 127.5, 129.2, 136.2 (CHAr), 128.4 (2×CHAr), 129.2 (2×CHAr), 122.9 (CF_3), 126.6 (C–CF_3), 125.9, 134.1, 138.0, 147.7, 161.5 (C). Anal. calcd for $C_{20}H_{18}F_3N$: C, 72.93; H, 5.51; N, 4.25. Found: C, 73.03; H, 5.60; N, 4.17; and **7cb**, oil; ^1H NMR: 0.94 (t, 3H, *J*=6.6 Hz), 1.51 (m, 4H), 2.07 (m, 1H), 2.49 (m, 2H), 2.75 (m, 2H), 3.12 (m, 1H), 3.43 (br s, 1H, D_2O), 6.55 (d, 1H, *J*=8.7 Hz), 7.13–7.37 (m, 7H); ^{13}C NMR: 14.5 (CH_3), 19.2, 29.2, 34.4, 39.2 (CH_2), 36.6, 54.3 (CH), 113.1, 124.5, 126.5, 127.3 (CHAr), 128.8 (2×CHAr), 129.5 (2×CHAr), 118.2 (CF_3), 119.7 (C–CF_3), 118.9, 140.6, 146.5 (C). Anal. calcd for $C_{20}H_{22}F_3N$: C, 72.05; H, 6.65; N, 4.20. Found: C, 72.12; H, 6.79; N, 4.13.

From **3db**, reaction time 10 h, SiO_2 eluent: from hexane–Et_2O 5:1 to Et_2O, afforded compounds **5db**, mp 134–136°C (white crystals from Et_2O–hexane); IR: 1440, 1360 cm^{-1}; ^1H NMR: 2.54 (s, 3H), 7.52 (m, 3H), 7.62 (m, 2H), 7.85 (d, 1H, *J*=8.4 Hz), 8.13 (m, 2H), 8.26 (d, 1H, *J*=8.4 Hz); ^{13}C

NMR: 21.1 (CH_3), 124.8, 125.1, 129.0, 130.9, 137.8 (CHAr), 128.8 (2×CHAr), 129.2 (2×CHAr), 126.1 (CF_3), 129.0 (C–CF_3), 126.9, 131.2, 140.7, 148.0, 163.1 (C). Anal. calcd for $C_{17}H_{12}F_3N$: C, 71.08; H, 4.21; N, 4.88. Found: C, 71.16; H, 4.33; N, 4.80; and **7db**, mp 78–80°C (white crystals from hexane); IR: 3400, 1610, 1529 cm^{-1}; ^1H NMR: 0.84 (d, 3H, *J*=7.0 Hz), 2.33 (m, 1H), 2.54 (dd, 1H, *J*=7.3, 16.2 Hz), 2.95 (dd, 1H, *J*=4.4, 16.2 Hz), 4.51 (br s, 1H, D_2O), 4.58 (d, 1H, *J*=3.6 Hz), 6.58 (d, 1H, *J*=8.8 Hz), 7.25–7.35 (m, 6H), 7.70 (m, 1H); ^{13}C NMR: 15.8 (CH_3), 31.7, 59.7 (CH), 33.3 (CH_2), 113.1, 124.6, 127.1, 128.6 (CHAr), 127.5 (2×CHAr), 127.8 (2×CHAr), 118.0 (CF_3), 119.5 (C–CF_3), 119.9, 142.2, 147.2 (C). Anal. calcd for $C_{17}H_{16}F_3N$: C, 70.09; H, 5.54; N, 4.81. Found: C, 70.20; H, 5.63; N, 4.70.

From **3eb**, reaction time 6 h, SiO_2 eluent: hexane–CH_2Cl_2 1:1, afforded compounds **5eb**, oil; IR: 1453 cm^{-1}; ^1H NMR: 1.28 (t, 3H, *J*=7.3 Hz), 2.27 (q, 2H, *J*=7.3 Hz), 7.58 (m, 5H), 7.87 (dd, 1H, *J*=1.8, 9.1 Hz), 8.21 (d, 1H, *J*=1.8 Hz), 8.28 (s, 1H), 8.49 (d, 1H, *J*=9.1 Hz); ^{13}C NMR: 16.9 (CH_3), 24.6 (CH_2), 120.7 (CF_3), 125.2, 125.9, 127.9, 129.5, 137.2 (CHAr), 127.8 (2×CHAr), 129.3 (2×CHAr), 127.1 (C–CF_3), 126.3, 137.5, 139.0, 147.9, 160.2 (C). Anal. calcd for $C_{18}H_{14}F_3N$: C, 71.75; H, 4.68; N, 4.65. Found: C, 71.84; H, 4.79; N, 4.59; and **7eb**, mp 85–87°C (cream crystals from Et_2O–hexane); IR: 3311, 1665, 1454 cm^{-1}; ^1H NMR: 0.94 (t, 3H, *J*=7.3 Hz), 1.95 (m, 1H), 2.05 (m, 1H), 2.39 (1H, m), 2.53 (dd, 1H, *J*=9.1, 16.2 Hz), 2.88 (dd, 1H, *J*=4.4, 16.2 Hz), 3.55 (br s, 1H, D_2O), 4.60 (d, 1H, *J*=3.7 Hz), 6.60 (m, 1H), 7.20–7.40 (m, 7H); ^{13}C NMR: 15.7 (CH_3), 24.1, 32.4 (CH_2), 35.2, 60.1 (CH), 113.7, 124.9, 127.5, 128.4 (CHAr), 128.2 (2×CHAr), 128.3 (2×CHAr), 119.0 (CF_3), 121.5 (C–CF_3), 120.1, 142.3, 147.5 (C). Anal. calcd for $C_{18}H_{18}F_3N$: C, 70.81; H, 5.94; N, 4.59. Found: C, 70.90; H, 6.02; N, 4.49.

From **3fb**, reaction time 6 h, SiO_2 eluent: from hexane–Et_2O 10:1 to Et_2O, afforded compounds **5fb**, mp 47–48°C (crystals from Et_2O–hexane); IR: 1452 cm^{-1}; ^1H NMR: 1.96 (m, 4H), 3.03 (t, 2H, *J*=6.6 Hz), 3.17 (t, 2H, *J*=6.6 Hz), 7.80 (dd, 1H *J*=1.8, 8.8 Hz), 7.90 (s, 1H), 8.04 (d, 1H *J*=1.8 Hz), 8.08 (d, 1H, *J*=8.8 Hz); ^{13}C NMR: 20.5, 25.6, 27.5, 27.7 (CH_2), 124.5, 125.9, 127.2, 136.1 (CHAr), 122.7 (CF_3), 127.0 (C–CF_3), 123.9, 131.2, 147.1, 161.2 (C). Anal. calcd for $C_{14}H_{12}F_3N$: C, 66.93; H, 4.81; N, 5.57. Found: C, 67.01; H, 4.90; N, 5.50; and **7fb**, mp 98–99°C (crystals from Et_2O–hexane); IR: 3424, 1619, 1519 cm^{-1}; ^1H NMR: 1.45 (m, 4H), 1.62 (m, 4H), 1.99 (m, 1H), 2.56 (dd, 1H, *J*=4.0, 16.2 Hz), 2.91 (dd, 1H, *J*=5.5, 16.2 Hz), 3.57 (m, 1H, *J*=3.7 Hz), 3.91 (br s, 1H, D_2O), 6.45 (d, 1H, *J*=8.8 Hz), 7.19 (d, 1H, *J*=8.8 Hz), 7.17 (s, 1H); ^{13}C NMR: 20.8, 24.8, 27.3, 31.8, 32.7 (CH_2), 32.5, 50.2 (CH), 118.9, 146.9 (C), 127.0, 124.2, 112.5 (CHAr), 122.1 (CF_3) 120.9 (C–CF_3), Anal. calcd for $C_{14}H_{16}F_3N$: C, 65.87; H, 6.32; N, 5.49. Found: C, 65.96; H, 6.40; N, 5.37.

From **3gb**, reaction time 18 h, SiO_2 eluent: hexane–CH_2Cl_2 1:1, afforded compound **5gb**, mp 231–233°C (cream crystals from hexane); IR: 1458 cm^{-1}; ^1H NMR: 3.14 (t, 2H, *J*=6.6 Hz), 3.46 (t, 2H, *J*=6.6 Hz), 3.99 (s, 2H), 7.86 (dd, 1H, *J*=1.8, 9.1 Hz), 7.97 (s, 1H), 8.10 (d, 1H, *J*=1.8 Hz), 8.13 (d, 1H, *J*=9.1 Hz); ^{13}C NMR: 26.6, 30.1, 34.8 (CH_2), 124.2 (CF_3), 125.2, 125.6, 130.0, 134.5 (CHAr), 128.0 (C–CF_3), 126.5, 130.9, 148.2, 160.9 (C). Anal. calcd for $C_{13}H_{10}F_3NS$: C, 57.98; H, 3.74; N, 5.20. Found: C, 58.10; H, 3.83; N, 5.10.

1.1.5. Synthesis of 2-(4-benzyl-3-methyl-5-oxo-5*H*-isoxazol-2-yl)-pyridine-3-carbaldehyde 8. To a solution of **1′a** (5 mmol) in DMF (4 ml) the 2-fluoro-pyridine-3-carbaldehyde[23] was added. The mixture was heated to 50°C for 4 h, then the reaction was diluted with brine (20 ml) and extracted with Et_2O (2×20 ml). The organic layer was dried, filtered and evaporated and the residue purified by silica gel column chromatography, eluent hexane–Et_2O 1.1 to give compound **8**, yield 60%, mp 108°C (white crystals from Et_2O). IR: 1738, 1690, 1633, 1490 cm^{-1}; ^1H NMR: 2.40 (s, 3H), 3.74 (s, 2H), 7.34 (m, 5H), 7.47 (m, 1H), 8.38 (dd, 1H, *J*=2.2, 8.8 Hz), 8.63 (dd, 1H, *J*=2.2, 4.8 Hz), 10.55 (s, 1H); ^{13}C NMR: 14.1 (CH_3), 28.6 (CH_2), 107.2, 126.7, 138.6, 152.7, 160.9, (C), 170.7 (CO), 124.5, 127.0, 138.4, 153.3 (CHAr), 128.7 (2×CHAr), 129.1 (2x CHAr), 188.9 (CHO). Anal. calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.25; H, 4.88; N, 9.45.

1.1.6. Synthesis of [1,8]naphthyridine 9 and tetrahydronaphthyridine 10. To a solution of compound **8** (2 mmol) in AcOEt (25 ml) 10% Pd/C was added and the mixture was hydrogenated under atmospheric pressure and rt. After 4 h the catalyst was filtered off, the solvent evaporated and the crude material was chromatographed, eluent CH_2Cl_2–Et_2O 3:1, to give compound **9**,[24] yield 68%, mp 123–125°C (white crystals from Et_2O–hexane); IR: 1630, 1490 cm^{-1}; ^1H NMR: 2.77 (s, 3H), 4.20 (s, 2H), 7.20 (m, 2H), 731–7.47 (m, 4H), 7.78 (s, 1H), 8.10 (dd, 1H, *J*=2.2, 8.0 Hz), 9.06 (dd, 1H, *J*=2.2, 4.4 Hz), ^{13}C NMR: 24.1 (CH_3), 39.0 (CH_2), 121.6, 126.9, 136.4, 136.5, 152.9 (CHAr), 129.0 (2×CHAr), 129.1 (2×CHAr), 121.7, 134.4, 138.6, 155.2, 162.9 (C). Anal. calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02, N, 11.96. Found: C, 82.13; H, 6.10; N, 11.89; and compound **10**, yield 13%, oil; ^1H NMR: 1.91 (tt, 2H, *J*=5.9, 6.2 Hz), 2.31 (s, 3H), 2.69 (t, 2H, *J*=6.2 Hz), 3.41 (t, 2H, *J*=5.9 Hz), 3.84 (s, 2H), 5.36 (br s, 1H, D_2O), 6.95 (s, 1H), 7.18 (m, 2H), 7.26–7.36 (m, 3H); ^{13}C NMR: 31.3 (CH_3), 20.5, 26.0, 36.8, 41.3 (CH_2), 127.0, 141.9 (CHAr), 128.4 (2×CHAr), 129.2 (2×CHAr), 120.6, 121.6, 138.4, 155.3, 160.4 (C). Anal. calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.71; H, 7.70; N, 11.69.

When the catalytic hydrogenation reaction was performed in EtOH the ratio between **9** and **10** was 24 and 74%.

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References

1. Beccalli, E. M.; Marchesini, A. *J. Heterocycl. Chem.* **1980**, *17*, 763–765.

2. Beccalli, E. M.; Marchesini, A. *J. Org. Chem.* **1987**, *52*, 3426–3434.
3. Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis* **1991**, 127–131.
4. Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis* **1991**, 861–862.
5. (a) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synth. Commun.* **1993**, *23*, 685–702. (b) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Tetrahedron* **1998**, *54*, 14401–14406.
6. Dubè, D.; Blouin, M.; Brideau, C.; Chan, C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Tagari, P.; Young, R. N. *Biorg. Med. Chem. Lett.* **1998**, *8*, 1255–1260.
7. Kalluraya, B.; Sreevinasa, S. *Farmaco* **1998**, *53*, 399–404.
8. Maguire, M. P.; Sheets, K. R.; Mc Vety, K.; Spada, A. P.; Zilberstein, A. *J. Med. Chem.* **1994**, *37*, 2129–2137.
9. (a) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467–477. (b) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203–206. (c) Kobayashi, K.; Yoneda, K.; Mizumoto, T.; Umakoshi, H.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **2003**, *44*, 4733–4736. (d) Huma, H. Z. S.; Halder, R.; Kaltra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488. (e) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209–6211. (f) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Moreno-Manas, M.; Vallribera, A. *Tetrahedron Lett.* **2002**, *43*, 5537–5540. (g) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *59*, 2507–2514.
10. (a) Jones, G. *Quinolines. The Chemistry of Heterocyclic Compounds*, Wiley: London, 1977; Vol. 32. (b) Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chem. Eur. J.* **2000**, 2513–2522.
11. Ashok, K.; Sridevi, G.; Umadevi, Y. *Synthesis* **1993**, 623–626.
12. (a) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1988**, *44*, 6225–6234. (b) Beccalli, E. M.; Benincori, T.; Marchesini, A. *Synthesis* **1988**, 630–631. (c) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1997**, *53*, 10433–10440.
13. (a) Panizzi, L. *Gazz. Chim. Ital.* **1946**, *76*, 44–55. (b) Parrini, V.; Pepino, R.; Belgodere, E. *Gazz. Chim. Ital.* **1974**, *104*, 715–729.
14. Murahashi, S.; Imada, Y.; Hirai, Y. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2968–2976.
15. Silveira, Jr. A.; Satra, S. K. *J. Org. Chem.* **1978**, *44*, 873–874.
16. Jacquier, R.; Petrus, C.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1970**, 2685–2690.
17. Beccalli, E. M.; Gelmi, M. L.; Marchesini, A.; Pilati, T. *J. Org. Chem.* **1987**, *52*, 1666–1669.
18. Boulton, A. J.; Katritzky, A. R. *Tetrahedron* **1961**, *12*, 41–50.
19. Wallingford, V. H.; Homeyer, A. H.; Jones, D. M. *J. Am. Chem. Soc.* **1941**, *63*, 2252–2254.
20. Katritzky, A. R.; Oksne, S.; Boulton, A. J. *Tetrahedron* **1962**, *18*, 777–790.
21. Bennet, G. M.; Scorah, L. V. D. *J. Chem. Soc.* **1927**, 194–200.
22. Berde, H. V.; Gogte, V. N.; Tiak, B. D. *Indian J. Chem.* **1972**, *10*, 332–336.
23. Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 48–56.
24. See Ref. 9a.